DRUG NAME: Everolimus

SYNONYM(S): 40-O-(2-Hydroxy)ethyl-rapamycin,[1] RAD001[2]

COMMON TRADE NAME(S): AFINITOR®

CLASSIFICATION: miscellaneous

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Everolimus is an inhibitor of mTORC1 (mammalian target of rapamycin complex 1). This complex plays an essential role in protein synthesis downstream of the P13K/AKT pathway, which is dysregulated in many human cancers. Everolimus has been shown to reduce cell proliferation, glycolysis, and angiogenesis in solid tumours *in vivo*.[1] Everolimus is cell cycle phase-specific. It inhibits cell proliferation by blocking cell cycle progression from the G1 phase to the S phase.[1-3] Everolimus is an immunosuppressive agent.[3]

PHARMACOKINETICS:

Oral Absorption	rapid[4]; 30% bioavailability[4]; high fat meals may reduce Cmax (60%) and AUC (16%)	
Distribution	time to peak: 1-2 hours	
	cross blood brain barrier?	yes
	volume of distribution	20% confined to plasma; tissue distribution not defined
	plasma protein binding	74%
Metabolism	extensively metabolized by CYP 3A4[4]	
	active metabolite(s)	none
	inactive metabolite(s)	6 main metabolites; three monohydroxylated metabolites, two hydrolytic ring-opened metabolites, and a phosphatidylcholine conjugate
Excretion	mainly biliary/fecal (as metabolites)	
	urine	5%
	feces	80%
	terminal half life[4]	30 hours
	clearance	5-55 L/h
Ethnicity	higher clearance in blacks	

Adapted from standard reference[3] unless specified otherwise.

USES:

Primary uses:

* Breast cancer
* Neuroendocrine tumour
* Renal cell carcinoma

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to everolimus or other rapamycin derivatives (i.e., sirolimus, temsirolimus)[3,5]

Caution:
- AFINITOR DISPERZ® tablets for oral suspension contain the ***same active ingredient*** as AFINITOR® tablets; however these dosage forms are ***NOT interchangeable***. Tablet formulations are approved for different indications and differ in strength.[6]
- ***Immunosuppression*** induced by everolimus may predispose patients to bacterial, fungal, viral or protozoal ***infections,*** including infections with opportunistic pathogens. Hepatitis B reactivation has been reported. Pre-existing infections should be treated and fully resolved before starting everolimus.[3]
- ***Vaccination*** may be less effective due to diminished immune response.[3] Live vaccines and close contact with individuals who have received live vaccines should be avoided to reduce the risk of infection from the vaccine.[3,7]
- ***Impaired wound healing*** is a class effect of the rapamycins. Exercise caution during the peri-surgical period.[3]
- High potential for ***drug interactions*** due to CYP 3A4 or P-glycoprotein.[3,7]

Carcinogenicity: not oncogenic in animal studies[3]

Mutagenicity: not clastogenic or mutagenic in genotoxicity studies; further details not available.[3]

Fertility: Animal studies indicate that male fertility is reduced, but may be reversible. Testicular morphology is affected and sperm motility, sperm count, and plasma testosterone levels are diminished. In animal studies, female fertility is not affected.[3]

Pregnancy: FDA Pregnancy Category D.[7] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective). In animals, embryo-fetal toxicities, including increased resorptions, decreased numbers of live fetuses, reduced fetal weight, increased malformations (i.e., sternal cleft), and skeletal variations, are reported. Women of childbearing potential and men with partners of childbearing potential should use medically acceptable contraception throughout treatment and continue 8 weeks after their last dose.[3]

Breastfeeding is not recommended due to the potential for secretion into breast milk. In animal studies, everolimus and/or its metabolites readily pass into breastmilk.[3,7]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[8,9] When placebo-controlled trials are available, adverse events are included if the incidence is >5% higher in the treatment group.[3]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (38-92%, severe 10-13%)
	hemorrhage (3%)
	leucopenia (3%)
	lymphopenia (8-51%; severe 18%)
	neutropenia (14%; severe <1%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	thrombocytopenia (7-23%; severe 1%)
cardiac	chest pain (5%)
	congestive cardiac failure (1%)
	tachycardia (3%)
endocrine	exacerbation of pre-existing diabetes (2%); new onset diabetes (<1%)
eye	conjunctivitis (2%)
	eyelid edema (4%)
gastrointestinal	*emetogenic potential: low*[10]
	abdominal pain (9%)
	diarrhea (30%, severe 1%)
	dry mouth (8%)
	dysphagia (4%)
	hemorrhoids (5%)
	mucosal inflammation (19%, severe 1%)
	nausea (26%, severe 1%)
	stomatitis (44%, severe <5%); see paragraph following **Side Effects** table
	taste alteration (10%)
	vomiting (20%, severe 2%)
general disorders and administration site conditions	chills (4%)
	fatigue (31%, severe 5%)
	peripheral edema (25%, severe <1%)
	pyrexia (20%, severe <1%)
	weight loss (9%)
immune system	***hypersensitivity reaction***; including anaphylaxis, dyspnea, flushing, chest pain, or angio-edema
infections and infestations	bronchitis (4%)
	infections (37%, severe <10%); see paragraph following **Side Effects** table
	nasopharyngitis (6%)
	pneumonia (6%)
	sinusitis (3%)
	urinary tract infection (5%)
investigations	ALT increase (3-21%, severe 1%)
	alkaline phosphatase increased (37%)[7]
	AST increase (3-25%, severe <2%)
	hyperbilirubinemia (3%, severe <2%)
	hypercholesteremia (20-77%, severe 3-4%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hyperglycemia (12-57%, severe 6-16%)
	hypertriglyceridemia (15-73%, severe 1%)
	hypocalcemia (3%)
	hypophosphataemia (5-37%, severe 6%)
	serum creatinine increase (9-50%, severe 1%)
metabolism and nutrition	anorexia (25%, severe 1%)
	asthenia (33%, severe <4%)
	dehydration
musculoskeletal and connective tissue	jaw pain (3%)
	extremity pain (10%, severe 1%)
nervous system	dizziness (7%)
	headache (19%, severe <2%)
	paresthesia (5%)
psychiatric	insomnia (9%)
renal and urinary	renal failure (3%)
respiratory, thoracic and mediastinal	***cough*** (30%, severe <1%)
	dyspnea (24%, severe <7%)
	epistaxis (18%)
	pharyngolaryngeal pain (4%)
	pleural effusion (7%)
	pneumonitis, non-infectious (14%, severe 4%); see paragraph following **Side Effects** table
	rhinorrhea (3%)
skin and subcutaneous tissue	acneiform dermatitis (3%)
	dry skin (13%, severe <1%)
	erythema (4%)
	hand-foot syndrome (5%)
	impaired wound healing (<1%)
	nail disorder (9%); including nail breakage
	pruritus (14%, severe <1%)
	rash (29%, severe 1%)
	skin lesion (4%)
vascular	hypertension (4%)

Adapted from standard reference[3] unless specified otherwise.

Localized and systemic infections, including pneumonia and other bacterial infections, invasive fungal infections, and viral infections, have been reported in up to 37% of patients. Infections are sometimes severe, leading to respiratory or hepatic failure, and fatalities have been reported. Prompt diagnosis and treatment of infection is important. Consider interruption or discontinuation of everolimus treatment. If invasive systemic fungal infection occurs, discontinue everolimus.[3]

Non-infectious pneumonitis, reported in 14% of patients, is a class effect of rapamycin derivatives. Severe and fatal cases have been reported. Symptoms include hypoxia, pleural effusion, cough or dyspnea. Patients should be advised to promptly report any new or worsening respiratory symptoms. Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue without dose alteration. If symptoms are moderate to severe, consider treatment interruption until symptoms improve. Corticosteroids may be indicated. Everolimus may be reinitiated at a reduced dosage of 5 mg daily based on patient response.[7]

Stomatitis is a class effect associated with mTOR inhibition. It presents as aphthous-like oral lesions, characterized as superficial, discrete ulcers with a white or gray center and a well-marked erythematous halo. Ulcerations are typically grade 1 or 2 in severity, but occur with relatively high incidence. In severe cases, stomatitis can interfere with oral intake and cause difficulty speaking. Onset tends to be early, within 2 to 3 weeks of treatment start; however, later onset (within 2 months) has also been documented. Symptoms typically resolve within a few weeks with effective management. Treatment options include topical, systemic, or intralesional corticosteroids with/without everolimus dose reduction or discontinuation. Prophylactic use of dexamethasone mouthwash has also been shown to reduce the incidence of grade 2 or worse stomatitis when used regularly during the first 8 weeks of everolimus treatment. Sodium bicarbonate solutions or oral antifungal agents do not appear to be effective for treatment or prevention of stomatitis.[11-14]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
ACE inhibitors[15-19]	increased incidence of angioedema	unknown[20,21]	avoid concurrent use if possible; monitor for signs of angioedema such as swelling of lips, tongue, or throat
cyclosporine[3,7,22]	increased AUC and Cmax of everolimus (possibly dependent on cyclosporine formulation); increased serum creatinine and increased risk of thrombotic disorders	moderate inhibition of P-glycoprotein by cyclosporine; possible competitive inhibition of CYP 3A4 by everolimus	monitor renal function and blood concentrations of both; may reduce everolimus dose to 5 mg, a further dose reduction to 5 mg every other day may be required; cyclosporine dose adjustments may also be required
erythromycin[3,7,22]	increased Cmax and AUC of everolimus	moderate inhibition of CYP 3A4 and P-glycoprotein by erythromycin	avoid if possible; if used concurrently, may reduce everolimus dose to 5 mg, a further reduction to 5 mg every other day may be required
grapefruit juice[3,7,22]	may increase plasma level of everolimus	may inhibit CYP 3A4 metabolism of everolimus in the intestinal wall	avoid grapefruit and grapefruit juice during treatment
ketoconazole[3,7,22]	increased Cmax, AUC, and half-life of everolimus	strong inhibition of CYP 3A4 and P-glycoprotein by ketoconazole	avoid if possible

AGENT	EFFECT	MECHANISM	MANAGEMENT
live vaccines[3,7,22]	diminished therapeutic effect of vaccine, increased susceptibility to vaccinial infections	possibly decreased ability to generate a humoral response to the vaccine	avoid vaccination during treatment and for 3 months following[4]
rifampin[3,7,22]	increased clearance and reduced Cmax and AUC of everolimus	strong induction of CYP 3A4 and P-glycoprotein by rifampin	avoid if possible; may consider increasing everolimus dose[4]
verapamil[3,7,22]	increased Cmax and AUC of everolimus	moderate inhibition of CYP 3A4 and P-glycoprotein by verapamil	avoid if possible; if used concurrently, may reduce everolimus dose to 5 mg, a further dose reduction to 5 mg every other day may be required

Everolimus is a substrate of CYP 3A4 enzyme and a substrate and moderate inhibitor of the efflux transport protein P-glycoprotein. Absorption and subsequent elimination of everolimus may be influenced by agents affecting CYP 3A4 and/or P-glycoprotein. Co-administration with strong inhibitors or inducers of either CYP 3A4 or P-glycoprotein should be avoided if possible. Co-administration with moderate inhibitors of CYP 3A4 or P-glycoprotein require monitoring for increased side effects and consideration of possible everolimus dose reduction.[3]

In vitro, everolimus is also a competitive inhibitor of CYP 3A4 and a mixed inhibitor of CYP 2D6. Full dose studies have not been done. Clinical significance is unknown.[3]

SUPPLY AND STORAGE:

Oral**:** Novartis Pharmaceuticals Canada Inc. supplies everolimus (AFINITOR®) as 2.5 mg, 5 mg, and 10 mg tablets. Tablets contain lactose. Store at room temperature. Protect from light and moisture.[3]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

Oral:[3,23-26] ***10 mg PO once daily.***

Administer on an empty stomach or after a small fat-free meal, at the same time each day (preferably in the morning).
Do not crush or chew tablets.

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"

Dosage in renal failure: no dose adjustment required[3]

BC Cancer usual dose noted in ***bold, italics***

Dosage in hepatic failure:

modify according to protocol by which patient is being treated; if no guidelines available, the following has been suggested[23,27]:

Degree of Impairment	Dose (PO daily)*
mild (Child-Pugh A)	7.5 mg; decrease to 5 mg if not tolerated
moderate (Child-Pugh B)	5 mg; decrease to 2.5mg if not tolerated
severe (Child-Pugh C)	max 2.5 mg

*Alternately, a universal 50% dose reduction has been used in mild to moderate hepatic failure.[1,3]

Dosage in dialysis:

no information found

Children:

has been used[23,28,29]

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